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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,132	03/14/2001	Christen M. Anderson	660088.420D5	7823

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EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,132	ANDERSON ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58,60 and 64-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *58,60 and 64-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *5-30-01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

Applicant's election of Group VII, claims 58-74 in the Response filed December 3, 2003, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Status of the Claims

Claims 1-57, 59, 61-63, and 75 –112 have been cancelled. Therefore, Claims 58, 60, 64-74 are pending and have been considered on the merits in this Office Action.

Objection for lack of Sequence Compliance Withdrawn

The objection to the disclosure because of a lack of sequence identifiers for the sequences listed in Figures 1A, 1B, and 2 is withdrawn in light of the amendment to the Brief Description of the Drawings.

Claim Objections--Withdrawn

Claims 58 and 72 are objected to because of the following informalities: Claims 58 and 72 refer only to the acronym "ANT". The full name of the polypeptide should be given in each independent claim. If desired, the acronym may be given in parenthesis after the full name and any dependent claim may refer to that acronym. For example, claim 58 should read "A method for determining the presence of an adenine nucleotide translocator (ANT) polypeptide". Appropriate correction is required.

Rejections Withdrawn

The rejection of Claims 58, 63-66, 71and 72 under 35 U.S.C. 102(b) as being anticipated by Schultheiss et al. (Clin. Exp. Immunol. (1983) 54: 648-654) is withdrawn in light of the amendment to the claims. Schultheiss et al. teach an assay to detect bovine ANT and not human ANT.

The rejection of Claims 58, 63-66, 70, and 72-73 under 35 U.S.C. 102(b) as being anticipated by Brandolin et al. (FEBS LETT (1974) 46(1): 149-153; ref. BC of IDS of Paper No. 5) is withdrawn in light of the amendment. Brandolin et al. teach an assay to detect rat ANT and not human ANT.

The rejection of Claims 58, 63, 70, 72, and 73 under 35 U.S.C. 102(b) as being anticipated by Bojanovski et al. (Eur. J. Biochem. (1976) 71: 539-548; ref. AM of IDS of Paper No. 5) is withdrawn in light of the amendment to the claims. Bojanovski et al. teaches an assay to detect rat ANT and not human ANT.

The rejection of Claims 58, 63-66, and 71-72 under 35 U.S.C. 102(b) as being anticipated by Klingenberg et al. (Biochim. Biophys. Acta (1978) 503: 193-210; ref. BJ of IDS of Paper No. 5) is withdrawn in light of the amendment to the claims. Klingenberg et al. teaches an assay to detect bovine ANT and not human ANT.

The rejection of claims 59 under 35 U.S.C. 103(a) as being unpatentable over Schultheiss et al. (Clin. Exp. Immunol. (1983) 54: 648-654) in view of Fiore et al. (Biochimie (1998) 80: 137-150; ref. BG in IDS of Paper No. 5) is withdrawn in light of the cancellation of the claim.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A response to Applicants arguments follows a restatement of the rejection as it applies to the amended claims.

Rejection:

The claim appears to be drawn to a method of determining the presence of ANT1, or ANT2, or ANT3 in a sample using a ligand binding assay. Alternatively, as implied by Applicants Response filed December 3, 2003, the claim encompasses detecting one or more of specifically ANT1, ANT2, ANT3. However, the prior art, as evidenced by Stepien et al. (J. Biol. Chem. (1992) 267(21): 14592-14597), teaches that ANT1 is *predominantly* in skeletal and cardiac muscles (but is also expressed in Brain and Kidney) and ANT2 (at low levels) and ANT3 are expressed in all tissues tested (see p. 14594, Table I). Thus, a large number of tissues express at least one adenine nucleotide translocator. Moreover, there are additional ANT isoforms such as ANT4 (see WO 99/07845; ref. AG of IDS of Paper No. 5). The presently claimed method does

not have any steps that would allow differentiation between whether the binding of the ANT ligand represents ANT1, ANT2, or ANT3 or other isoforms such as ANT4 or isoforms not yet discovered. Therefore, in samples containing more than one isoform (which would be almost all samples since ANT2 is expressed in all tissues) determination of which ANT isoform was present in a sample could not be determined using the claimed method. In the instant case, undue experimentation would be required to determine the presence of ANT1, ANT2 or ANT3 specifically using the claimed method because the claimed method does not have a step to identify the ANT isoform. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The nature of the invention

The nature of the invention involves the discovery of atractyloside derivatives having various substitutions at the 6' hydroxyl (see Specification pages 92-122) and their use in methods of detection and purification of adenine nucleotide translocators. The claim involves a method of detecting ANT1, ANT2, and/or ANT3 in a sample by a binding assay using an atractyloside derivative (a ligand that binds adenine nucleotide translocators generally).

The amount of direction or guidance presented

The present Specification provides a generic description of a method of detecting adenine nucleotide translocators but does not teach how to differentiate between which ANT polypeptide (of ANT1, ANT2, ANT3 or another ANT isoform) was detected.

The presence or absence of working examples

The present Specification does not provide any working examples that describe how one would differentiate between whether ANT1, ANT2, ANT3, or another adenine nucleotide translocator was detected.

The state of the prior art and relative skill of those in the art

As evidenced by Brandolin et al. (FEBS LETT (1974) 46(1): 149-153; ref. BC of IDS of Paper No. 5), Bojanovski et al. (Eur. J. Biochem. (1976) 71: 539-548; ref. AM of IDS of Paper No. 5).and Klingenberg et al. (Biochim. Biophys. Acta (1978) 503: 193-210; ref. BJ of IDS of Paper No. 5), it appears that the binding affinity of ANT polypeptides with atractyloside and its derivatives were very well known in the art. Furthermore, it was very well known in the art to use this binding affinity in methods of purification and detection. However, a thorough search of the art did not reveal any teachings of how to use atractyloside and its derivatives to determine which isoform of ANT is in a particular sample. Moreover, a thorough search of the art did not reveal any antibodies or other ANT ligands that are specific for a particular ANT isoform and do not react with the others. Fiore et al. (Biochimie (1998) 80: 137-150; ref. BG in the IDS of Paper No. 5) teach that the sequences for ANT1, ANT2, and ANT3 were well known in the art (see p. 139-142) and were highly similar. Therefore, the level of skill of those in

the art would allow expression and purification of the ANT isoforms but would not allow prediction as to whether atractyloside derivatives or any other ligands would have unique interactions with each of the ANT isoforms to allow differentiation between them in a method of detection.

The predictability or unpredictability of the art

Since the interaction and binding characteristics of atractyloside and its derivatives or any other ANT ligand with each of the ANT isoforms was unknown at the time of the invention, it would be highly unpredictable to use the claimed method to determine the presence of any particular ANT isoform in a sample.

Quantity of Experimentation

A large quantity of experimentation would be required to find a ligand that would specifically bind to an individual ANT isoform so as to allow differentiation of which ANT isoform is in a sample.

To practice the instant invention would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the discovery of an ANT ligand that would bind specifically to a particular ANT isoform and not to any other ANT polypeptides. It is this additional characterization of each ANT isoform and its ligand, required to practice the claimed method, which constitutes undue experimentation.

Response to Applicants arguments:

Applicants argue that as amended Claim 60 relates to detection of any one or more of the recited ANT polypeptides. This argument has been considered but is not

deemed persuasive for the following reasons. First, as indicated below in the rejection under 35 U.S.C. 112, second paragraph, the claim is unclear as to whether it relates to one of the ANT subtypes or more than one of the ANT subtypes. Second, in either case, the claim is not enabled for the reasons stated above. As stated in the previous Office Action, there are additional ANT isoforms such as ANT4 (see WO 99/07845; ref. AG of IDS of Paper No. 5). The presently claimed method does not have any steps that would allow differentiation between whether the binding of the ANT ligand represents ANT1, ANT2, or ANT3 or *other isoforms such as ANT4 or isoforms not yet discovered.* Thus, while one of skill in the art could use the claimed method to detect ANT polypeptides in general, one of skill in the art could not use the claimed method, which lacks a step that identifies the bound ANT polypeptide, to detect a specific ANT isoform.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 58, 64-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultheiss et al. in view of Boulay et al. (Anal. Biochem. (1983) 128: 323-330; ref. AO of IDS filed 3-14-01). Fiore et al., Rosenburg (Protein Analysis and Purification: Benchtop Techniques (1996) Birkhauser, Boston, MA, pp. 170-182 and 303-322), and Osman et al. (J. Immunol. Methods (1993) 161(1): 97-106).

Schultheiss et al. teach a method of determining the presence of an adenine nucleotide translocator from bovine liver mitochondria samples during different steps of its purification. In the purification method, samples containing ANT are contacted with ^{3}H-carboxyatractyloside to allow for binding. Then, during the purification of ANT, the ^{3}H-carboxyatractyloside samples containing the adenine nucleotide translocator bound to the detectable ^{3}H-carboxyatractyloside are detected using the radiolabel thereby allowing the determination of which sample contains the ANT polypeptide. (see pp. 649, lines 19-22).

Schultheiss et al. uses radiolabeled atractyloside derivative in the method of detection and does not teach a fluorescently labeled atractyloside. Schultheiss et al. teaches the detection and isolation of bovine ANT and not human ANT.

Boulay et al. teaches the chemical synthesis of fluorescent derivatives of atractyloside wherein the 6' hydroxyl is substituted with several different fluorescent

substituents including dansyl aminobutyryl (a 6' hydroxyl with an amine containing functionality). Boulay et al. teach that atractyloside is very susceptible to modifications of the functional groups in the molecules except the primary alcohol group of the glucose disulfate moiety (the 6' hydroxyl). Thus, contrary to Applicants assertion (Response filed 12-3-03, p. 10, first paragraph), it was well recognized in the art at the time of the invention that the 6' hydroxyl of atractyloside could be substituted without significantly altering the binding of atractyloside to ANT as evidenced by Boulay et al..

Fiore et al. teach the involvement of adenine nucleotide translocator in myopathies and suggest the use of fluorescently labeled atractyloside to detect the amount of ANT within the mitochrondria in order to screen for ANT deficiencies (p. 147, Col. 2 and p. 148, last sentence). Fiore et al. states that the fluorescent approach is much more sensitive than the radioactive assay since it requires approximately 100 times less biological material (p. 147, Col. 2).

Rosenburg teaches that radiolabeling, biotinylating, and fluorescent labeling a ligand of the protein of interest are functionally equivalent means for detecting proteins (section spanning 170-171; see also "Biotin-Avidin System", p. 171-172, "Detection of Radiolabeled Proteins", pp. 176-178, and pp. 178-179). Rosenburg teaches that the various isotopes are functionally equivalent in the detection of proteins using a radiolabeling method (see p. 177). In addition, how the ligands are bound to the solid phase (covalently or non-covalently) are also functionally equivalent (pp. 303-322).

Osman et al. teach that Eu3+ is a known and widely used type of fluorophore in the detection of proteins. As taught by Osman et al. an Eu3+ labeled polyclonal

antibody is available that can be used with a streptavidin-biotin detection system. Thus, Osman et al. demonstrates that Eu3+ is functionally equivalent to other detection systems such as biotin, radiolabeling, other fluorescent labels, etc.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use the method of Schultheiss et al. to determine the presence of or purify human ANT in human samples as suggested by Fiore et al. One of ordinary skill in the art would have been motivated to use a method of detecting an ANT specifically in human samples (containing human ANT) in order to further the understanding of the relationship of ANT to mitochondrial myopathy as suggested in Fiore et al. Furthermore, one of skill in the art would have recognized that the 6' hydroxyl could be substituted with a variety of detectable labels. Those of skill in the art recognized the 6' hydroxyl of atractyloside as a preferred position for substitution with labeled substituents as evidenced by Boulay et al. and Fiore et al. As evidenced by the prior art discussed above, one of ordinary skill in the art at the time of the invention was readily aware of all of the various protein detection systems such as radiolabeling, biotinylating, and fluorescence labeling. Also, as evidenced in the prior art, it was well within the skill of the art at the time of the invention to choose the type of labeling that would suit the particular assay at hand. Therefore, for example, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Schultheiss et al. by using fluorescently labeled atractyloside derivative as suggested in Fiore et al. and specifically taught in Boulay et al. One of ordinary skill in the art would have had motivation to use a fluorescent label in methods of detecting the

amount of ANT in patients with myopathies because high sensitivity (which the fluorescent label would allow) would be necessary in these particular situations.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 60 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 60, as amended, is unclear as to whether the claim is intended to encompass only one ANT subtype or at least one ANT subtype. The phrase "wherein the human adenine nucleotide translocator polypeptide" implies that the method detects the binding of a ligand to a specific ANT subtype (e.g. ANT1, or ANT2, or ANT3) since the claim from which it depends (Claim 58) refers to "*a* human ANT". In addition, the Markush language is alternative language that implies a single species (ANT1 or ANT2 or ANT3). However, the transitional phrase "comprises" implies that more than one ANT subtype is intended (e.g. ANT1 and/or ANT2 and/or ANT3). Applicants response also implies that the claimed method is drawn to detecting one or more of ANT1, ANT2, or ANT3 (see Response filed December 3, 2003, p. 7, paragraph 3).

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Tuesday, Thursday, and Friday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
February 26, 2004

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